Comm.
Dr. Gardner
Dr. Loosli
Dr. Sommers

CHRONIC PULMONARY DISEASES

#808R2
#808R1-4/1/72-3/31/73
#808-4/1/71-3/31/72

THE COUNCIL FOR TOBACCO RESEARCH—U.S.A., INC.

110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

Application For Renewal of Research Grant
(Use extra pages as needed)

First Renewal ☐ Second Renewal ☒

Date: Jan. 17, 1973

RECEIVED
JAN 29 1973

1. Principal Investigator (give title and degrees):

Allen Barry Cohen, M.D., Ph.D., Assistant Professor of Medicine

2. Institution & address:

University of California Service
San Francisco General Hospital
1001 Potrero Street
San Francisco, California 94110

3. Department(s) where research will be done or collaboration provided:

Department of Medicine

4. Short title of study:

Human Alveolar Macrophages and Emphysema

5. Proposed renewal date: April 1, 1973

6. How results to date have changed earlier specific research aims:

No changes since 1972 renewal application.

7. How results to date have changed earlier working hypothesis:

No changes.

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Source: https://www.industrydocuments.ucsf.edu/docs/nfpl0000

8. Any additional facilities now required? Describe briefly:

No increased facilities needed.

Please see attached page for details of additional equipment needs.

9. Any changes in personnel? Append biographical sketches of new key professional personnel:

No changes in professional personnel.

Laboratory technician added in April, 1972: Ralph Knight, BS biochemistry, Washington University, Seattle. Two years experience in Lab of Neurath and Wilcox.

10. Append outline of experimental protocol for ensuing year.

11. List publications or papers in press resulting from this or closely related work. (append reprints or manuscripts not previously sent).

see attached list

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12. Summary progress report (append in standard form as separate document, unless recently submitted)

Source: https://www.industrydocuments.ucsf.edu/docs/

13. Budget for the coming year:

A. Salaries (give names or state "to be recruited")	% time	Amount
Professional (give % time of investigator(s) even if no salary requested)		
Allen B. Cohen	35	-0-
Technical		
Ralph Knight	50	-0-
Sub-Total for A		-0-

B. Consumable supplies (by major categories)

Animals for antisera - $1000

Chemicals including enzymes and substrates - $2000

Small miscellaneous equipment and consumable supplies - $2000

Sub-Total for B $5,000

C. Other expenses (itemize)

Travel (one Eastern meeting)	$500
Publication costs	$250
Equipment maintenance	$1000

Sub-Total for C $1,750

Running Total of A + B + C $6,750

D. Permanent equipment (itemize)

pH Stat - Radiometer

Sub-Total for D $4,724

E. Indirect costs (15% of A+B+C) E $1,013

Total request $12,487

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14. Other sources of financial support:

List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Alpha-1-antitrypsin: Does it inhibit an enzyme which causes emphysema?	National Heart and Lung Institute, NIH (SCOR) HL 14201	34,117	12/1/72 to 11/30/73

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
NONE			

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Allen B. Cohen, M.D., Ph.D.

Signature Allen B. Cohen Date 11/1/73

Telephone 415 (Area Code) 648-8200 (Number) 273 or 627 (Extension)

Checks payable to

Regents of the University of Calif.

Mailing address for check:

1487 Fourth Avenue

San Francisco, Calif. 94122

Responsible officer of institution

Typed Name Leona M. Butler

Title Gifts and Endowments Officer

Signature _____ Date _____

Telephone 415 (Area Code) 666-2047 (Number) (Extension)

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8. Additional Requirements:

While the spectrophotometer has filled our needs for enzymes and alpha-1-antitrypsin analysis to date, it has severe limitations because only substrates which change their optical absorbance spectrum can be used. A full examination of the human alveolar macrophage enzyme inhibited by alpha-1-antitrypsin will necessitate an exploration of its actions against selected artificial substrates. This work requires a pH stat.

In addition, our investigations on the biochemical mechanism of alpha-1-antitrypsin (also credited to 808R) are now in a phase which requires examination of enzyme kinetics for artificial substrates in the presence of chromagenic reagents. Such kinetic analysis can only be done with a pH stat.

I am, therefore, requesting a pH stat for the 03 year of 808R. Since my research technician previously funded on 808R is now funded on the NIH grant, the total amount of funds requested will approximate the amount requested in the initial application. If the salary savings ($1,800) from the late hiring of Mr. Knight in the 02 year of 808R can be carried to the 03 year, the requested budget will not exceed needs projected in the initial application.

pH Stat - Radiometer Components

III - pH meter and controller		$1,138
PHA - 943 Titrigraph module		298
SBR 3		1,260
ABU 12-T with Burette B 220		821
Burette B230		108
Thermal jacket V 526		42
Console D 764		48
TTA - 31 Titration Assemblies		596
PHA 940 Two channel titrator module		166
	Subtotal	$4,477
5.5% State Sales Tax		247
	Total	$4,724

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Source: https://www.industrydocuments.ucsf.edu/docs/nfp0039

PART I: Protocol for continued investigations of enzymes which cause emphysema in alpha-1-antitrypsin deficient subjects.

I am continuing my efforts to localize enzymes in lung which bind to alpha-1-antitrypsin. Antibodies to alpha-1-antitrypsin are being labeled with rhodamine in order to search for enzymes in lung which bind to alpha-1-antitrypsin.

In recent months an abstract was published by Galdston (1) which indicated that elastase is deficient in neutrophils from patients who have a deficiency of alpha-1-antitrypsin and do not have emphysema. This may be an important observation. If a genetic deficiency in neutrophil elastase, by itself, prevents the emphysema from developing in patients deficient in alpha-1-antitrypsin, then it is reasonable to assume that the missing elastase contributes a major share of the lung damage which develops in patients deficient in alpha-1-antitrypsin. If the observation can be confirmed, one might suspect that an inhibitor of this enzyme would prevent the emphysema which these patients develop. It is, therefore, important for other laboratories to confirm Galdston's observation. Since the original protocol was designed to identify enzymes which could cause emphysema in patients deficient in alpha-1-antitrypsin, I will test Galdston's observation in two siblings who have Pi Type ZZ deficiency in alpha-1-antitrypsin and no evidence of emphysema.

PART II: Protocol for continuation of the study of the biochemical mechanism of alpha-1-antitrypsin.

Niecamp (2) has used a polyacrylamide gel electrophoretic technique to determine the conditions which will provide maximal shift of enzyme inhibitor complex toward the free enzyme and altered inhibitor with a cleaved peptide bound at the carboxyl side of the inhibitory site. I will try to establish these conditions for alpha-1-antitrypsin. The amino acid which can then be released by carboxypeptidase (3) will then indicate the amino acid at the inhibitory site of alpha-1-antitrypsin which binds to each enzyme. If these data establish that all enzymes act at a limited number of amino acid sites in a manner similar to the manner that enzymes bind to amino acids in their substrates, then I can begin to develop inhibitors which act on the same enzymes that alpha-1-antitrypsin acts on.

References:

1. Galdston, M., C. Gottwalt, A.L. Davis, and A. Janoff: Fed.Proc. 31:282, 1972.

2. Niecamp, C., H. Hixson and M. Laskowski: Biochem. 8:16, 1969.

3. Ozawa, K. and M. Laskowski: J. Biol. Chem. 241:3955, 1966.

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Source: https://www.industrydocuments.ucsf.edu/docs/[illegible]

11. Publications or papers in press resulting from this or closely related work:

1. Cohen, A.B. and Cline, M.J.: The human alveolar macrophage: Isolation cultivation in vitro and studies of morphologic functional characteristics. J. Clin. Invest. 50:1390, 1971.

2. Mann, P., Cohen, A.B., Finley, T., and Ladman, J.: Alveolar macrophages: Structural and functional differences between nonsmokers and smokers of marijuana and tobacco. Lab. Invest. 25:111, 1971.

3. Murray, J.F., Cohen, A.B., Gold, W., and Greenspan, R.: Early diagnosis of obstructive lung disease. Calif. Med. 116:37, 1972.

4. Cohen, A.B.: The human alveolar macrophage: Isolation, cultivation in vitro and studies of morphologic and functional characteristics. Dissertation for Doctor of Philosophy. December, 1972.

5. Cohen, A.B. and Cline, M.J.: In vitro studies of the foamy macrophage of postobstructive endogenous lipoid pneumonia in man. Am. Rev. Resp. Dis. 106:69, 1972.

6. Cohen, A.B., and Cline, M.J.: Human alveolar macrophages: Functional differences between smokers and nonsmokers. Abstract Clin. Res. 18:483, 1970.

7. Cohen, A.B.: A new hypothesis for the mechanism of action of alpha-1-antitrypsin and supporting experiments. Clin. Res. 20:575, 1972 *

8. Cohen, A.B.: Biochemical mechanism of action of alpha-1-antitrypsin. Submitted to J. Biol. Chem. 1972

9. Cohen, A.B.: Interrelationships between human alveolar macrophages and alpha-1-antitrypsin. Submitted to J. Clin. Invest. 1973.

10. Cohen, A.B.: Purification of two populations of human alveolar macrophages. Submitted to Am. Rev. Resp. Dis. 1973.

* This work received the Cecile Lehman Mayer Research Award for basic sciences of pulmonary diseases in 1972 by the American College of Chest Physicians.

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